the patients of the '559 patent do not resist inhalation; according to the Examiner, the reference meets the limitations of the present claims because the method of the present claims and the process of administration of an effective dose of insulin in the '559 patent both involve oral administration of insulin. Applicant respectfully traverses this rejection.

The '559 patent discloses delivery of insulin to the lungs, not delivery of the formulation to the buccal cavity. As established in the Declaration of Pankaj Modi, a method which describes delivery of a formulation to the lungs cannot also be a method in which inhalation is resisted. On the contrary, a formulation that delivers a drug to the lungs requires that a patient inhale the formulation. The '559 patent can be said to "teach away" from resisting inhalation, as it requires the opposite action to provide an effective dose of the composition described in that patent.

Also as established in the Declaration, the method disclosed in the '559 patent, and supported by data therein, simply cannot result in delivery of an effective amount of insulin to the buccal region of oral cavity, as does the method of the present invention. The '559 patent discloses that over 80% of the formulation is delivered to the lungs; any remaining amount (which is not residing in the device itself) is not enough to provide an effective dose of insulin. As described in the Declaration, due to the nature of the drug and the illness being treated, insulin delivery requires a known and precise dosage. The method of administration described in the '559 patent cannot provide this, and cannot provide an effective amount, as would be understood by one skilled in the art. Therefore, Claims 26, 27 and 37 are not anticipated by the '559 reference. Applicant respectfully requests withdrawal of this basis of rejection.

Rejections Under 35 U.S.C. § 103

Claims 26-27, 29 and 37 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Manning, '559, and as unpatentable over Radhakrishnan (5,049, 389). According to the Examiner, both the '559 and '389 patents teach

pulmonary administration of the disclosed compositions, which would inherently result in buccal administration. Applicant respectfully traverses this rejection.

As described above, the '559 patent does not teach or suggest delivery of an effective amount of insulin, either explicitly or inherently. As established in the declaration, pulmonary administration cannot result in an effective amount of insulin delivered to the buccal region. A method which teaches pulmonary delivery also cannot teach resisting inhalation, as recited in the claims of the present invention; it teaches the opposite, that is, one must inhale to benefit from the composition. The '559 patent provides no guidance whatsoever on buccal delivery of insulin, nor would one skilled in the art look to a disclosure on pulmonary administration for information on how to deliver a drug by the methods of the present invention. Applicant respectfully submits that the present invention is not obvious in view of the '559 patent and requests withdrawal of this basis of rejection.

The '389 patent is also cited for teaching pulmonary administration which, according to the Examiner, would inherently result in buccal administration. Applicant respectfully submits that the present invention is patentable over the '389 patent; all arguments presented above are equally applicable to this reference. The Declaration establishes that the '389 patent does not teach resisting inhalation, and it does not teach delivery of an effective amount of insulin to the buccal cavity, either explicitly or inherently. Applicant respectfully submits that Claims 26-27, 29 and 37 are not obvious in view of the '389 patent and requests withdrawal of this basis of rejection.

Double Patenting Rejection

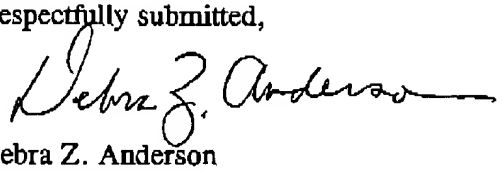
Applicant files in connection with this response a terminal disclaimer over U.S. Patent 6,221,378 (Application Serial No. 09/386,285) to obviate any question of double patenting.

SUMMARY

In view of the above arguments, the declarations and the terminal disclaimer, Applicant respectfully submits that all pending claims, Claims 26-34 and

36-37 are in condition for allowance; such action is respectfully requested at an early date.

Respectfully submitted,



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Re: U.S.S.N. 09/538,829, Filed: March 30, 2000

Entitled: "Method for Administering Insulin to the Buccal Region"

Attorney Docket No.: 358594-00010-2

Attorney: Debra Z. Anderson, Esquire Phone 412.566.1910
Eckert Seamans Cherin & Mellott
600 Grant Street, 44th Floor - Pittsburgh, PA 15219

Enclosed: Response To Office Action ; Declaration of Pankaj Modi
Fee Transmittal
Terminal Disclaimer
Request for One Month Extension of Time

9/ Declaration

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application Of	: Group Art Unit: 1615
PANKAJ MODI	: Examiner: T. Ware
Serial No. 09/538,829	: Attorney Docket No. 358594-00010-2
Filed: March 30, 2000	:
	: Entitled:
	: METHOD FOR ADMINISTERING INSULIN TO THE BUCCAL REGION

DECLARATION OF PANKAJ MODI

I, Pankaj Modi, being duly sworn hereby declare as follows:

1. I have a Master of Science degree in Chemical Engineering (Brooklyn Polytechnic University, U.S.A., 1976); a Master of Science degree in Polymeric Materials / Biomedical Sciences (Brooklyn Polytechnic University, U.S.A., 1976); a Master of Business Administration degree (University of Dallas, U.S.A., 1978); and a Doctorate (Ph.D.) in Biomedical Sciences / Biopolymeric Materials (University of Toronto, 1992). I did additional Post-Doctorate training at McMaster University in the Department of Neuroscience / Psychiatry.

2. Since October of 1996 to the present I have been employed at Generex Pharmaceuticals, Inc., 22 Harbour Square, Suite 202, Toronto, Ontario, Canada M5J 2G2 where I am Vice President of Research and Development. In my position as Vice President of Research and Development, I am responsible for, among other things, new drug development, including all testing (including oversight of clinical trials) associated with new drug development.

3. From 1994 (prior to the time I joined Generex Pharmaceuticals, Inc.) to the present, I have been involved in the research and development of novel drug delivery systems. I have developed various delivery systems for oral and/or nasal delivery of drugs including non-steroidal anti-inflammatories, vaccines, interferons and hormones and other pharmaceutical agents to be used in the treatment of a variety of diseases. A primary focus of my research while at Generex has been

the development of an oral delivery system for insulin and other large molecule drugs.

4. I am a member of the following professional societies: American Diabetes Association; Canadian Diabetes Association; Society of Endocrinology; American Association of Pharmaceutical Scientists; Indian Association of Pharmaceutical Scientists; and the Professional Chemical Engineers Society.

5. I have been a named inventor on 19 U.S. patents/patent applications.

6. I am the named inventor of the invention set forth in the claims of the above-captioned application

7. I participated in the preparation of the above-captioned application and claims, read the same thoroughly before the case was filed, and I have recently re-read and reviewed the application and claims of the case.

8. I have carefully read the Office Action dated July 12, 2001, which included rejection of the claims under 35 U.S.C. § 102(e) as anticipated by Manning et al. (5,770,559), and the rejection of the claims under 35 U.S.C. § 103(a) as obvious in view of the Manning and Radhakrishnan (5,049,389) references.

9. The present invention is directed to a method for delivering insulin compositions to the buccal region of the oral cavity. According to the methods of the present invention, a patient self-administering the insulin composition will resist inhalation of the spray, to ensure delivery of the drug to the buccal region. When inhalation is resisted, over 80 percent of the aerosol is delivered to the oral cavity; less than 10% is delivered to the gastrointestinal tract or the lungs (some of the formulation remains in the device).

10. As is known to anyone developing new modes of insulin delivery for diabetics, delivery of insulin requires very precise dosage. Delivery of too much insulin can result in hyperglycemic shock; delivery of too little insulin results in the opposite, hypoglycemic shock. Either situation can be life-threatening. Thus, it is essential that any mode deliver a predictable and known amount of the drug. A method in which the residual dose from a completely different method of administration (to the lungs) may or may not be delivered to the buccal cavity, where it may or may not be absorbed, is not a method which can reliably deliver an effective

amount of insulin. Therefore, the method of the '559 patent cannot be said to teach delivery, either explicitly or inherently, of an effective amount of insulin to the buccal cavity.

11. The '559 patent discloses at column 15, lines 15-20, significant lung absorption, that is, greater than 80% of the formulation is utilized in the lungs. Therefore, the less than 20% remaining, a portion of which may still reside in the device itself, cannot be considered an effective amount of the drug, for purposes of the present invention. As noted above, delivery of an effective amount of insulin requires a precise and known amount of the drug.

12. The '559 patent discloses delivery of the formulation described therein to the lungs. With this mode of delivery, patients do not resist inhalation; on the contrary, they inhale as deeply as possible to draw the drug into the lungs. Patients receiving the drugs described in the '559 patent could not resist inhalation of the drug and receive an effective dose according to the methods of that invention.

13. In view of the fact that the method of administration described in the '559 patent requires inhalation of the composition, the '559 patent cannot be said to teach or suggest resisting inhalation, as recited in the claims of the present invention; in fact, it teaches the opposite. Similarly, the method of the '559 patent cannot result, either explicitly or inherently, in an effective amount of the drug being delivered to the buccal region of the oral cavity of a patient. It is my well considered opinion, therefore, that the '559 patent does not anticipate the claims of the present invention; it does not teach or suggest delivery of an effective amount of the drug to the buccal region of the oral cavity, while resisting inhalation.

14. The claims of the present invention were also rejected as obvious in view of the '559 patent. However, as described above, the '559 patent does not teach or suggest, either explicitly or inherently, that an effective amount of insulin can be delivered to the buccal region, while resisting inhalation. The '559 patent teaches lung delivery of the compositions therein; such delivery would require inhalation of the formulation and could not be administered to someone who was resisting inhalation.

15. The claims of the present invention were also rejected as obvious in view of the '389 patent. It is my well considered opinion, that this patent does not render obvious, the claims of the present invention.

16. As in the '559 patent, the '389 patent discloses delivery of a formulation to the lungs. Patients receiving the formulation described therein would not resist inhalation; they would inhale as deeply as possible to draw the drug into their lungs. Patients receiving the drugs described in the '389 patent could not resist inhalation of the drugs and receive an effective dose.

17. The examples of the '389 patent show that the majority of the drug is successfully administered to the lung, including the deep lung region. Table 9 of the '389 patent indicates that less than 20% of the formulation remains in the joint, throat or collar of the device, areas which *may* correspond to the oral cavity of a person, or alternatively, to residual amounts left in a device used by a patient. Therefore, the small amount remaining in the device cannot be considered an effective amount of the drug for purposes of the present invention.

18. In view of the above, the '389 patent does not teach or suggest spraying a composition while resisting inhalation, nor does it teach or suggest, explicitly or inherently, delivery of an effective amount of insulin to the buccal region. Therefore, it is my well considered opinion that the '389 patent does not render obvious the claims of the present invention.

19. Based on all of the above, it is my well considered opinion that the claims of the present invention are patentable over the '559 and '389 patents.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: Nov. 12, 2001 Pankaj Modi

Pankaj Modi